JMedSci

Journal of the Medical Sciences
(Berkala Ilmu Kedokteran)

Volume 55, Number 2, 2023; 99-107
https://doi.org/10.19106/JMedSci005502202301

Effects of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one on serum levels of antioxidant enzymes in hyperlipidemic rats

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Submitted: 2023-01-06
Accepted : 2023-04-02

ABSTRACT

Hyperlipidemia triggers oxidative stress caused by an imbalance between oxidant and antioxidant levels due to the excess production of reactive oxygen species (ROS). The increase of ROS can decrease antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). 7-OH-2-(4-OH-3-Methoxyphenyl)-chroman-4-one is exogenous antioxidants isolated from mahogany seeds (*Swietenia macrophylla* King). This study aimed to evaluate the effects of the 7-OH-2-(4-OH-3-methoxyphenyl)-chroman-4-one on serum levels of SOD, CAT, and GPx in hyperglycemic rats. Thirty-six male Wistar rats (Rattus norvegicus) were divided into the following six groups: (N) normal group, (HL) hyperlipidemia group, (P) hyperlipidemia group with simvastatin, F10, F30, and F90 hyperlipidemia group with 7-OH-2-(4-OH-3-methoxyphenyl)-chroman-4-one 10, 30 and 90 mg/200g body weight (BW), respectively. Hyperlipidemia was induced by feed enriched with cholesterol and cholic acid. Treatments were administered orally by gavages. After 4 weeks of treatments, blood sample was drawn and serum levels of SOD, CAT, and GPx enzymes were analyzed using a spectrophotometric method. Serum levels of SOD, CAT, and GPx in hyperlipidemic rats treated with 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one at dose 10, 30 and 90 mg/200g BW were higher than HL group. In addition, no significantly different on serum SOD and CAT between group F90 and group P was observed (p>0.05).

ABSTRAK

Hiperlipidemia dapat memicu stress oksidatif yang disebabkan oleh ketidakseimbangan antara senyawa oksidan dan kadar antioksidan akibat produksi reactive oxygen species (ROS) yang berlebih. Kenaikan ROS ini dapat menurunkan enzim antioksidan seperti superoksida dismutase (SOD), katalase (CAT) dan glutation peroksidase (GPx). Senyawa 7-OH-2-(4-OH-3-metoksifenil)-kroman-4-one adalah antioksidan eksogen yang diisolasi dari biji mahoni (*Swietenia macrophylla* King). Tujuan dari penelitian ini adalah mengkaji pengaruh pemberian senyawa 7-OH-2-(4-OH-3-metoksifenil)-kroman-4-one terhadap kadar SOD, CAT dan GPx dalam serum tikus hiperglikemia. Sebanyak 36 ekor tikus wistar (Rattus norvegicus) jantan dibagi menjadi 6 kelompok yaitu (N) kelompok normal, (HL) kelompok hyperlipidemia, (P) kelompok hyperlipidemia + simvastatin, F10, F30, dan F90 kelompok hyperlipidemia + 7-OH-2-(4-OH-3-metoksifenil)-kroman-4-one berturut-turut dengan dosis 10, 30 dan 90 mg/200g berat badan (BB). Tikus hiperglikemia dibuat dengan diinduksi makanan kaya kolesterol dan asam kolic. Enzim SOD, CAT dan GPx dianalisis menggunakan metode spektrofotometri. Kadar SOD, CAT, dan GPx serum tikus hiperlipidemia yang diberi 7-OH -2-(4-OH-3-metoksifenil)-kroman-4-one dosis 10, 30 dan 90 mg/200g BB lebih tinggi dibanding kelompok HL. Kadar SOD dan CAT serum kelompok F90 (dosis 90mg/200g BB) berbeda tidak bermakna dengan kelompok P (p>0,05).

Keywords:
hyperlipidemia:
superoxide dismutase;
catalase;
glutathione peroxidase;
antioxidants

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INTRODUCTION

Hyperlipidemia is a medical condition characterized by an increase in one or all of the lipid or lipoprotein profiles in the blood.[1] These conditions lead to the development of free radicals in the body that cause other pathological diseases. Hyperlipidemia is the most common cause of atherosclerosis which affects more than 3 million adults throughout the United States and Europe. Recently, the incidence of the atherosclerosis is rapidly increasing.[2] The decrease in antioxidants caused by reactive oxygen species (ROS) is a key factor for the initiation of the development of hyperlipidemia-related diseases such as atherosclerosis.[3] An imbalance between ROS production and the endogenous antioxidant systems can cause damage to cellular biomolecules, including lipids, proteins, and DNA.[4]

Several natural antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) act as radical scavengers which are biomolecular repair systems damaged by free radicals.[5] These enzymes act as an inhibitor of the oxidation process and also inhibit chain oxidant reactions at small concentrations so they can suppress the potential threat of pathological processes.[6] The SOD enzyme act as the first scavenger by catalyzing the superoxide anion into H_2O_2 and oxygen molecules.[7] The CAT enzyme is a tetrameric ferriheme oxidoreductase which catalyzes H_2O_2 into water and oxygen.[8] In addition, there is a debate on the role of CAT versus peroxynitrite, but recent advances reported the ability of CAT as an ONOO-scavenger.[9] The GPx enzyme is a selenium-dependent oxidoreductase that uses H_2O_2 or organic hydroperoxides as oxidants and tripeptide glutathione (GSH) as electron donors.[10]

Hyperlipidemia conditions can be treated through a pharmacological approach by considering the side effects associated with drugs. Several studies have examined natural ingredients that have active compounds such as polyphenols and flavonoids which have antioxidant and antihyperlipidemic activities.[11]

Mahogany seeds (*Swietenia macrophylla* King) have a variety of isolated pure compounds with a large number of pharmacological activities that have been identified and isolated. Some of these compounds have hypolipidemic and antioxidant activities.[12] One of the compounds that was successfully isolated from mahogany seeds was 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one which is a compound belonging to the flavonoid class which has many benefits including as antioxidant effect.[13] This study aimed to evaluate the antioxidant effects of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one by measuring serum antioxidant enzymes in hyperlipidemic rats.

MATERIALS AND METHODS

Compound tested

7-Hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one was isolated from S. macrophylla King by Dr. Sri Mursiti from the Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Negeri Semarang, Semarang.

Experimental design

Thirty-six male Wistar rats weighing between 150 and 200 g, 10 weeks old, were used in this study. Serum levels of SOD, CAT, and GPx were tested using a post-test only with a normal group design. The research location was conducted in two laboratories: The Biochemistry Laboratory, Faculty of Medicine, Public Health and Nursing,

Universitas Gadjah Mada, and the Food and Nutrition Laboratory, Universitas Gadjah Mada, Yogyakarta, Indonesia. The experiments were carried out according to the guidelines for the use of animals and approved by the Medical and Health Research Ethic Committee, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (No. KE/FK/08/8/EC/2017).

The rats were divided into 6 groups of experimental with 6 rats in each group with the following distribution: Normal group (N), hyperlipidemia group (HL), hyperlipidemia group with simvastatin 0.18 mg/200 g BW (P), hyperlipidemia group with 10 mg (F10), 30 mg (F30) and 90 (F90) mg/200 g BW 7-OH-2-(4-OH-3-methoxyphenyl) chroman-4-one, respectively. The rats were given AIN 93M standard feed for 5 days for acclimatization. Hyperlipidemia was induced by administering laboratory feed enriched with 10 g/kg cholesterol and 2 g/kg cholic acid for a week. Groups N and HL were given orally by infusion with the same volume of water, while the other groups were given 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one once daily for 4 weeks. At the end of the experiment, the serum samples were collected for assessment of SOD, CAT, and GPx serum levels.

Serum antioxidant measurement

The serum SOD level was measured by spectrophotometry in percentages. The CAT serum level (U/mL) was measured by spectrophotometry.[14] The GPx serum level (U/mL) was measured spectrophotometrically.

Statistical methods

The data were expressed as the mean ± standard deviation (SD). One-way Anova was used to examine the effects of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one on serum levels of SOD, CAT, and GPx. The p value <0.05 was used to determine significant differences between groups. Homogeneous variance with individual comparisons were obtained by Tukey's HSD post hoc test.

RESULTS

Serum level of SOD

The results showed that the cholesterol-induced rats (HL) had lower serum SOD levels than the normal group (N) (FIGURE 1). Serum SOD levels in hyperlipidemic rats that were intervened with 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one dose 10,30 and 90 mg/200g BW were higher than HL group that was not intervened. Serum SOD levels at the dose of 90 mg/200 gBW (F90) were not significantly different (p>0.05) compared with the simvastatin group (P).

Serum CAT levels

Serum CAT levels after administration of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one at doses 10, 30, and 90 mg/200gBW were higher compared to the hyperlipidemic group (HL) (FIGURE 2). Serum CAT levels at a dose of 90 mg/200gBB were not significantly different (p>0.05) compared with the simvastatin group (P).

Serum GPx levels

Serum GPx levels after administration of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one at doses 10, 30, and 90 mg/200gBW were higher compared to the hyperlipidemic group (HL) (FIGURE 3).

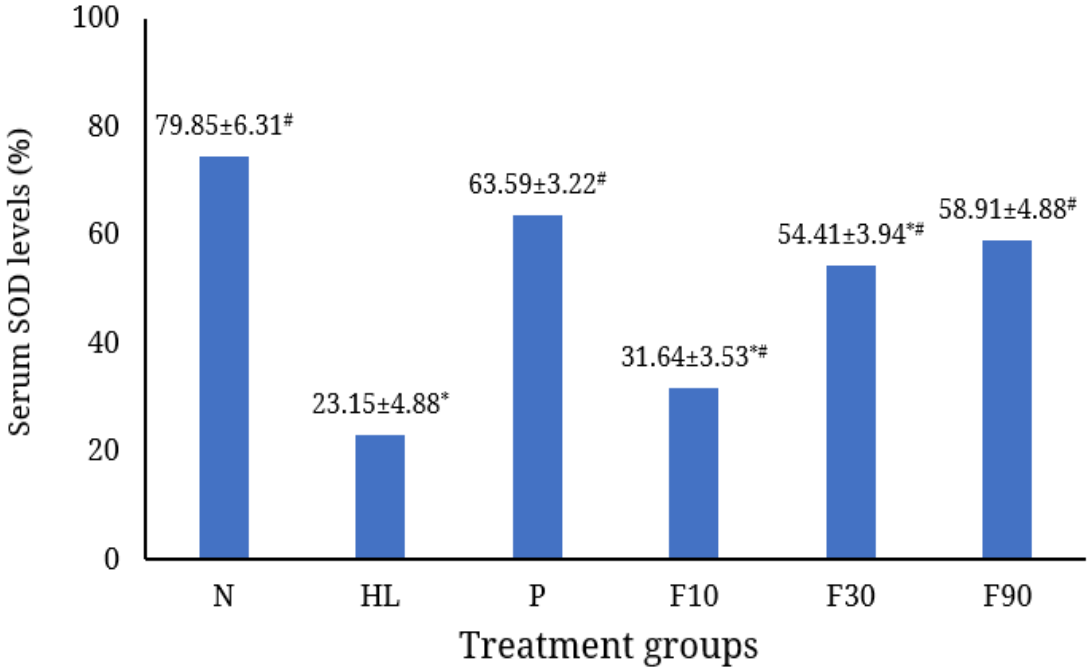

FIGURE 1. Serum SOD levels (%) in hyperlipidemic rats. N: normal, HL: hyperlipidemia, P: HL + simvastatin, F10, F30, F90: HL+ 7-OH-2-(4-OH3-methoxyphenyl)-chroman-4-one 10, 30, 90 mg/200g BW, respectively. Normality test with Shapiro-Wilk; data were tested with Anova test, Notation *: p <0.05 vs P; #: p <0.05 vs HL.

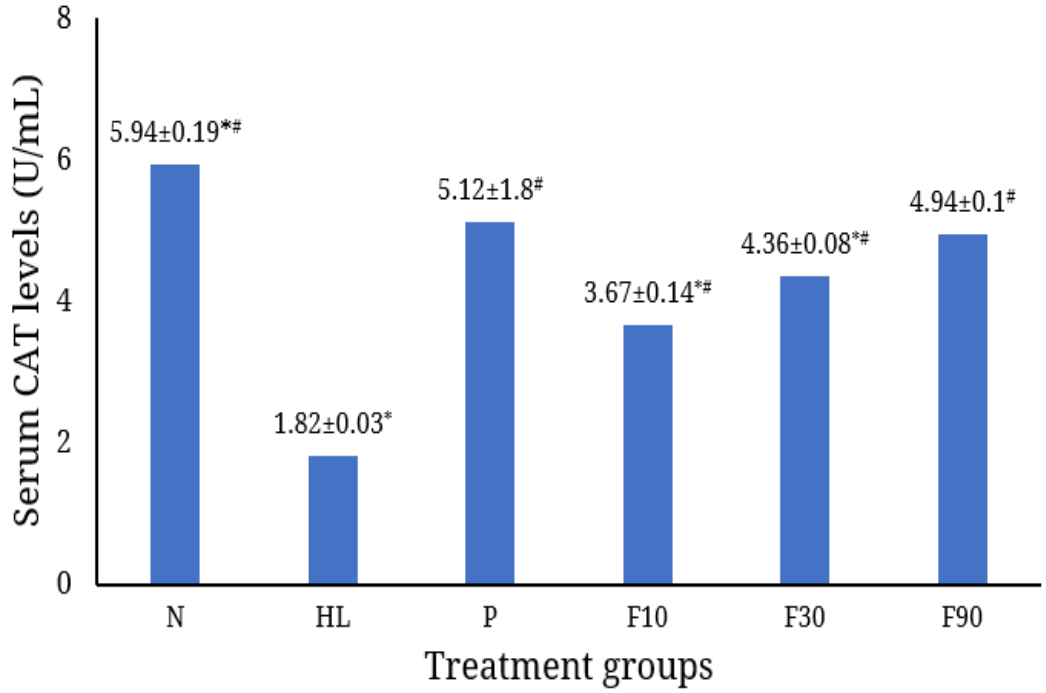

FIGURE 2. Serum CAT levels (U/mL) in hyperlipidemic rats. N: normal, HL: hyperlipidemia, P: HL + simvastatin, F10, F30, F90: HL+ 7-OH-2-(4-OH3-methoxyphenyl)-chroman-4-one 10, 30, 90 mg/200g BW, respectively. Normality test with Shapiro-Wilk; data were tested with Anova, p <0.05. Notation *: p <0.05 vs P; #: p <0.05 vs HL.

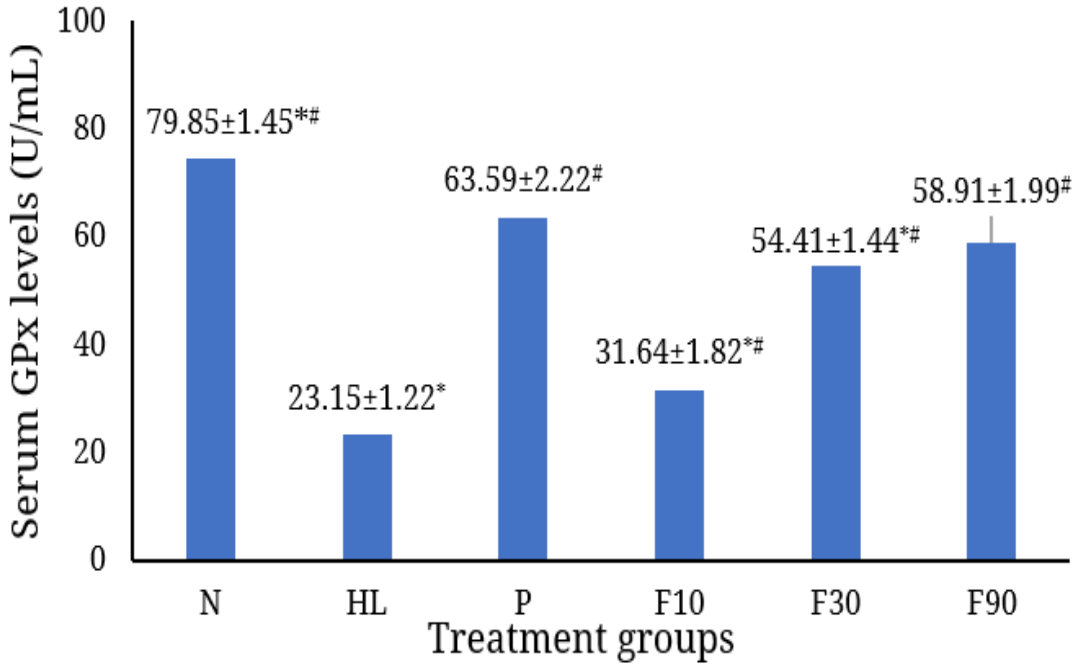

FIGURE 3. Serum levels of GPx (U/mL) in hyperlipidemic rats. N: normal, HL: hyperlipidemia, P: HL + simvastatin, F10, F30, F90: HL + 7-OH-2-(4-OH3-methoxyphenyl)-chroman-4-one 10, 30, 90 mg/200g BW, respectively. Normality test with Shapiro Wilk; data were tested with Anova p <0.05. Notation *: p <0.05 vs P; #: p <0.05 vs HL.

DISCUSSION

The high-fat diet for one week promotes hyperlipidemia as reviewed by Ayunda *et al.*,[15] who reported that cholesterol-induced rats had higher total and low-density lipoprotein (LDL) cholesterol than the normal group. Lipids are very susceptible to damage caused by free radicals which result in lipid peroxidation that causes adverse changes.[16]

High lipid levels change the properties of lipids and activate NADPH oxidase to produce ROS. High levels of fat and LDL can also suppress antioxidant enzymes.[17] This is in line with the results after induction of hyperlipidemia which showed lower serum antioxidant enzymes compared to the normal group. Increased lipid peroxidation and decreased antioxidant activity are the initial events in the development of hyperlipidemia.[18] Low antioxidant enzyme activity can also be associated with enzyme inactivation by ROS which causes damage to proteins.

Simvastatin is clinically proven to reduce blood cholesterol levels.[19] The simvastatin effectively inhibits HMG CoA reductase activity, thereby preventing cholesterol synthesis in the liver. Decreased cholesterol synthesis in the liver will affect the lipid profile in circulation.[20]

Flavonoids can reduce cholesterol levels by inhibiting the absorption of cholesterol in the intestines and can suppress increasing bile formation to be excreted with feces.[21] Both simvastatin and flavonoids have a positive effect on body fat balance. The 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one is a flavonoid isolated from mahogany seeds which is a class of flavanones. The positive effects of 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one on antioxidants and the body, especially in serum are reflected in the results of

post-intervention with 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one for 4 weeks which can increase serum antioxidant enzymes (SOD, CAT or GPx) in various dose groups compared to the hyperlipidemia group.

Serum level of SOD and Catalase at the dose of 90 mg/200gBW (F90) have the same effect with the simvastatin group (P) p>0.05. The increase in serum antioxidant enzymes is in line with the study of Wu *et al.*,[22] who administered extracted flavonoids from *Rhodomyrtus tomentosa* Hassk berries thereby increasing serum SOD and glutathione peroxidase (GSH-Px) levels and suppressing serum malondialdehyde (MDA) levels. Zeng *et al.*,[23] also conducted research related to the increase in serum antioxidants after the flavonoid intervention, which compared six different flavonoids, namely epicatechin, epigallocatechin, procyanidin, quercetin, taxifolin, and rutin given to rats with induced aging by D-galactose.

In addition to increasing antioxidant enzymes such as SOD, CAT, and G-Px, the studied flavonoids also suppress MDA and inflammatory markers such as tumor necrosis factor-alpha (TNF-α), Interleukin (IL)-1β and IL-6 which are caused by oxidative stress. The structural diversity of flavonoids is postulated to be an important element that influences their antioxidant activity.[24] Several previous studies have compared the antioxidant activity of subclasses of flavonoids with different structures and the results reported that: the position and number of hydroxyl groups,[25] degree of polymerization,[26] glycosylated compounds,[27] the combination of carbonyl groups and C2=C3 double bonds[28] affect antioxidant activity.

7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one belongs to the homoisoflavonoid group which is a naturally occurring oxygen heterocyclic compound having two aromatic rings and an additional carbon between rings B and C on the isoflavonoid framework.[29] The antioxidant activity of similar compounds using nitro blue tetrazolium (NBT) and 1.1-diphenyl-2-picrylhydrazyl (DPPH) which are free radical scavenging methods. So besides being able to encourage the expression of antioxidant enzymes such as SOD, CAT, and GPx, these compounds can also act directly as free radical scavengers.[30] The lack of antioxidant enzymes such as SOD was proven to promote lipid peroxidation and triglycerides in rat livers and fatty liver conditions.[31] The low catalase in circulation is associated with hyperhomocysteinaemia can increase myocardial wall dysfunction under ischemia reperfusion by excessive ROS production by increased lipid peroxidation.[32] The GPx deficiency can accelerate and modify the development of atherosclerotic lesions in mice.[33]

The results showed that the serum levels of SOD, CAT, and GPx in hyperlipidemic rats that were intervened with 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one were higher than HL group that was not intervened. This finding can prevent the development of other diseases that originate from hyperlipidemic conditions through flavonoids related to the regulation of antioxidant enzymes, and suppression of lipid peroxidation by antioxidant gene expression in circulation.

CONCLUSION

Serum levels of SOD, CAT, and GPx in hyperlipidemic rats that are intervened with 7-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-chroman-4-one at dose 10, 30, and 90 mg/200gBW are higher than HL group that is not intervened. Group F90 (dose 90 mg/200g BW) and group P (simvastatin) shows no significant difference in results on serum SOD and CAT.

ACKNOWLEDGEMENT

The authors wish to extend their thanks to all staff in the Biochemistry Laboratory at the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, and the Food and Nutrition Laboratory, Universitas Gadjah Mada for preparing the necessary materials during this study.

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